Unexpected vitamin K deficiency in hospitalized patients

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Summary: Twenty-seven patients developed vitamin K deficiency unexpectedly in the postoperative period or during hospitalization for a variety of medical conditions. Twenty-two of the patients were on antibiiotics. Nineteen were on no oral intake during part of their hospital stay, and the remainder had a poor food intake. Fifty percent developed vitamin K deficiency within seven days. It is suggested that the rapid onset of vitamin K deficiency in these patients may have been due to a combination of the use of multiple antibiotics and poor food intake.

Résumé: *Une insuffisance inattendue en vitamine K chez des malades hospitalisés*

Chez 27 malades, on a noté une insuffisance inattendue de vitamine K, soit au cours de la période postopératoire, soit durant leur séjour à l'hôpital où ils avaient été admis pour traitement de diverses pathologies purement médicales. Vingt-deux de ces malades recevaient des antibiotiques. Dix-neuf n'avaient rien pris par la bouche durant une partie de leur séjour et les autres avaient un apport alimentaire pauvre. La moitié des malades ont présenté l'insuffisance en vitamine K durant une période de sept jours. Nous croyons que la survenue rapide de cette carence chez nos malades peut être attribuée à l'emploi de plusieurs antibiotiques, associé à un régime déficient.

Vitamin K deficiency is usually suspected in the newborn and in patients with malabsorption or obstructive jaundice. This disorder is also well recognized in patients on a vitamin-K-deficient diet. In these patients, the deficiency has been reported to occur over a period of weeks and has been attributed to a combination of poor intake of vitamin K and impaired synthesis of the vitamin by intestinal flora.[1] We have been impressed with the frequency of this disorder and with the fact that it may develop within a few days postoperatively in patients with a poor food intake who are receiving antibiotics.

Patients and methods

The diagnosis of vitamin K deficiency was made in 27 patients who were seen over a period of 24 months. Fifteen patients were postoperative cases, 13 having had operations on the gastrointestinal tract and two, gynecological procedures. The 12 medical patients did not have a recognized cause for vitamin K deficiency. Fifteen of the 27 patients were referred because of abnormal bleeding; in 10 this was of major degree and required blood transfusions and in five it was minor bleeding. The defect in the 12 patients without bleeding was detected by screening coagulation tests.

Criteria for diagnosis

Vitamin K deficiency was suggested by the finding of a prolonged prothrombin time and activated partial thromboplastin time. The diagnosis was confirmed in all patients by the rapid and complete correction of the prothrombin time by the intravenous injection of vitamin K_1 oxide (Aquamephyton, 10 to 15 mg.). In 12 of the cases the diagnosis of vitamin K deficiency was confirmed by the detection of low levels of factors II, VII, IX and X. No patients had deficiencies of Factor V or VII, or of fibrinogen.

Coagulation tests

The prothrombin time was performed with Simplastin (Warner-Chilcott, Morris Plains, New Jersey) and

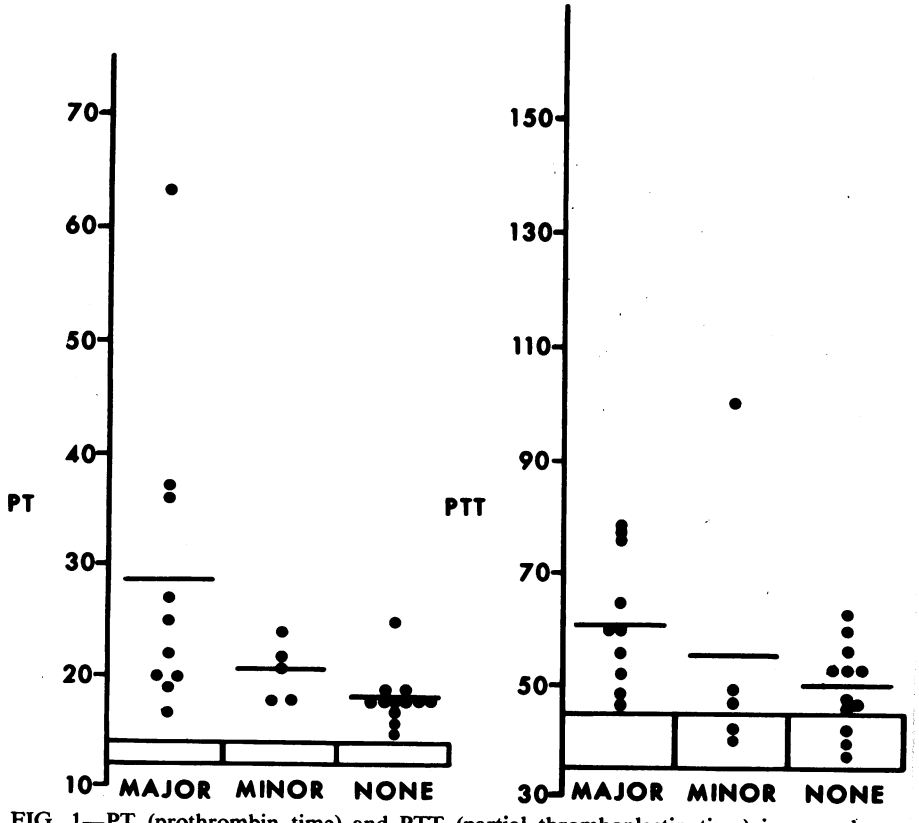

FIG. 1—PT (prothrombin time) and PTT (partial thromboplastin time) in seconds in relation to the bleeding manifestations: major — requiring blood transfusions, minor — bleeding not requiring blood transfusions, and none — no bleeding. Horizontal lines denote normal range.

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Table IA—Clinical presentation of patients with vitamin K deficiency postoperatively

Patient	Operation	Bleeding manifestations	Blood transfusions	Antibiotics (days)†	IV fluids (days)†	NPO* (days)†	PT‡ Pre	PT‡ Post	PTT‡ Pre	PTT‡ Post
D.M.	Cesarean section	Hematoma incision	2	A-8, PS-4	7	2	17	13	49	41
H.H.	Total gastrectomy	Upper GI hemorrhage	3	A-3, P & S-5	7	12	25	13	57	41
B.T.	Total gastrectomy	Upper GI hemorrhage	3	A-3, G & C-7	10	25	22	13	60	40
M.C.	Small bowel resection, mechanical obstruction	Upper GI hemorrhage, hematomas, IV sites	4	Nil	1	1	36	14	76	40
P.H.	Perforated peptic ulcer-laparotomy	Upper GI hemorrhage	3	A-10	10	13	20	14	52	38
S.O.	Mechanical small bowel obstruction	Incisional hematoma, nasogastric tube	2	Ch-4, Se-4	4	11	37	12	65	36
S.S.	Hysterectomy, small bowel resection	Upper GI hemorrhage, hematuria	2	A-6, C-12, E-6	21	23	27	14	77	39
C.C.	Total colectomy	Upper GI hemorrhage	0	A-10	8	7	22	12	100	40
F.H.	Abdominal hysterectomy	Hemoptysis, skin, venepuncture bleeding	0	G & C-4	4	6	21	14	41	37
J.P.	Bowel resection, diverticulitis	Upper GI hemorrhage	0	G & A-7, T-3	7	18	18	13	42	40
M.K.	Small bowel resection, Crohn's disease	Nil	0	G & C-7	10	8	18	13	41	33
A.L.	Revision colostomy	Nil	0	A-8, G & P-14	14	21	17	12	53	40
R.D.	Cholecystectomy	Nil	0	Nil	2	2	19	12	48	40
J.R.	Total gastrectomy	Nil	0	A & P-12	9	21	16	13	60	49
L.A.	Bowel obstruction, ischemic enterocolitis	Nil	0	A-6, G & C-10	22	22	18	13	46	40

*NPO = nothing per os.
†Number of days after operation before deficiency detected.
‡In seconds, records before and after vitamin K therapy.
A = ampicillin, PS = phenazopyridine HCl - sulfisoxazole, P = penicillin, S = streptomycin, G = gentamicin, C = cloxacillin, Ch = chloramphenicol, Se = Septrin (trimethoprim and sulfamethoxazole), E = erythromycin, T = tetracycline.

Table IB—Clinical presentation of medical patients with vitamin K deficiency

Patient	Diagnosis	Bleeding manifestations	Blood transfusions	Antibiotics (days)	IV fluids (days)	NPO* (days)	PT Pre	PT Post	PTT Pre	PTT Post
H.M.	Acute renal failure	Lower GI hemorrhage, epistaxis	4	Ga & K-4	4	3	63	13	78	40
R.P.	Progressive glomerulonephritis, peritoneal dialysis	Upper GI hemorrhage, epistaxis, hemoptysis	2	C & G-9, A-5	12	**	19	12	48	33
A.S.	Acute renal failure	Hematoma	1	A & C-10, Ce-9	14	19	20	14	60	50
J.N.	Acute renal failure	Petechiae, IV site bleeding	0	A-2, P & S-6	8	6	18	12	49	39
G.P.	Peritoneal dialysis	Bleeding around dialysis tube	0	Nil	10	**	24	13	47	40
J.H.	Peritoneal dialysis	Nil	0	Nil	7	**	15	12	63	36
K.R.	Membranous glomerulonephritis, hemodialysis	Nil	0	A-7	14	**	18	13	53	38
M.G.	Polycystic kidneys, peritoneal dialysis	Nil	0	Nil	2	**	18	14	56	38
D.K.	Chronic renal failure, pyelonephritis, hemodialysis	Nil	0	A-8	10	**	18	12	42	38
F.T.	*E. coli* septicemia	Nil	0	A-3, G & C-20	23	7	25	12	53	34
S.N.	Acute lymphocytic leukemia, pneumococcal pneumonia	Nil	0	G & C-6	14	4	19	13	40	40
L.M.	Meningococcal meningitis	Nil	0	A-2, C-1	5	2	18	13	38	34

*NPO = nothing per os.
**Poor intake during hospitalization.
Ga = gantrisin, K = kanamycin, C = cloxacillin, G = gentamicin, A = ampicillin, Ce = cephaloridine, P = penicillin, S = streptomycin.

a kaolin-activated partial thromboplastin time was performed by the method of Proctor and Rapaport.[2] Factors II, VII, IX, V and VIII were measured by the method described by Biggs and McFarlane[3] and Factor X was assayed by the method of Denson.[4] Plasma fibrinogen was measured by the method of Astrup, Brakman and Nissen.[5]

Results

The clinical and laboratory data of the 27 patients are summarized in Tables IA and IB. The most common site of bleeding was the gastrointestinal tract. The bleeding stopped rapidly when the coagulation defect was corrected with vitamin K in all but one patient (B.T.) who had an adenocarcinoma of the stomach and continued to bleed from the gastrointestinal tract. There was a correlation between the severity of bleeding and the degree of the hemostatic defect (Fig. 1). The prothrombin time was the most sensitive index of vitamin K deficiency, and all patients who had a prothrombin time of 25 seconds or more had major bleeding manifestations.

The factors possibly contributing to vitamin K deficiency in these patients were antibiotic therapy and poor oral intake; the details are shown in Tables IA and IB and are summarized in Table II. All of the postoperative patients had no oral intake during at least part of their postoperative course and none received vitamin K supplements. Thirteen were on antibiotics. One of the patients who did not receive antibiotics (M.C.) had known small-bowel disease but the other patient (R.D.) had been apparently normal preoperatively. Several patients had a poor food intake before as well as after admission, but this could not be assessed accurately. Renal insufficiency was the primary diagnosis in nine patients, while two others (F.H. and F.T.) had significant impairment of renal function.

The patients receiving antibiotics are divided in Table III into those with vitamin K deficiency detected after 0 to 7, 8 to 14 and more than 14 days of treatment. The most commonly used antibiotics were ampicillin, cloxacillin and gentamicin and these were often given in combination. In 20 of the 22 patients receiving antibiotics the parenteral route was employed, and in two patients both parenteral and oral antibiotic treatment was given.

Discussion

Decreased food intake and treatment with oral antibiotics are well recognized contributing factors to vitamin K deficiency.[1] Frick, Riedler and Brogli[6] studied patients sustained on intravenous fluids alone and found that vitamin K deficiency did not occur before five weeks of treatment. Some of these patients were also given neomycin orally, when vitamin K deficiency occurred after three to four weeks of treatment. Dearing, Mann and Needham[7] found that the prothrombin time was not significantly prolonged in ambulant patients after three to five days' treatment with broad-spectrum antibiotics in the usual doses. However, in patients treated in intensive care units with antibiotics and intravenous fluids, a prolonged prothrombin time developed within 12 to 21 days.[8]

In the present study we have shown that vitamin K deficiency, often resulting in serious bleeding, may occur unexpectedly in the early postoperative period and in patients with renal failure. It is likely that the more rapid onset of vitamin K deficiency in our postoperative patients was due to a combination of multiple antibiotic treatment and a poor oral intake, although two patients did not receive antibiotics and the cause of early vitamin K deficiency in one of them is uncertain. Some of our patients may have been marginally vitamin K-deficient before their admission to hospital, but no abnormal bleeding was encountered during operation, nor did it occur before admission in the medical patients. This suggests that the vitamin K deficiency developed during the patients' hospitalization.

The role of antibiotics in producing vitamin K deficiency is still unclear. The two known sources of vitamin K are food and colonic bacteria. Udall[9] showed that in patients on a vitamin-K-free diet and fixed doses of sodium warfarin, the use of neomycin, 4 g. daily for three weeks, led to only a slight elevation of the prothrombin time, suggesting that vitamin K derived from colonic organisms is not important.

It is unlikely that poor absorption alone could have accounted for the rapid onset of vitamin K deficiency in our patients. Antibiotics could possibly affect vitamin K metabolism in other ways, such as by impairment of uptake or utilization of the vitamin. For example, two drugs with antibiotic activity, namely cyclohexamide[10] and actinomycin D[11] have been shown to interfere with the hepatic production of vitamin-K-dependent clotting factors, but there is no evidence for this with the antibiotics used in our patients.

A striking feature was the frequency of vitamin K deficiency in patients

Table II—Factors contributing to vitamin K deficiency

	Number	Mean days*	Range
Total series			
Antibiotics	22	8.2	2-20
IV fluids	27	9.5	1-23
NPO	21	10.9	1-25
Postoperative			
Antibiotics	13	8.4	4-14
IV fluids	15	7.6	1-22
NPO	15	12.8	1-23
Medical			
Antibiotics	9	7.7	2-20
IV fluids	12	10.3	2-23
NPO	6	6.8	2-19

*Number of days on antibiotics, etc. from time of admission or operation until deficiency detected.

Table III—Development of vitamin K deficiency in patients on antibiotics

	Duration of antibiotic therapy before detection of deficiency		
	0-7 days	8-14 days	> 14 days
No. developing deficiency	11	10	1
No. on more than one antibiotic	10	6	1
Ampicillin	6	9	1
Cloxacillin	5	3	1
Gentamicin	5	3	1

with renal failure. This was the primary diagnosis in nine patients and two others had significant impairment of renal function. Only three of the patients were on chronic dialysis so that this is unlikely to be of etiological significance. Decreased levels of vitamin-K-dependent clotting factors in renal failure have been reported,[12,13] and it is probable that, in our patients, poor food intake and the frequent use of antibiotics were important contributing factors.

Since this was not a prospective study, it is difficult to estimate the frequency of vitamin K deficiency. However, in a 647-bed hospital in a period of 24 months there were 3106 surgical procedures performed on the gastrointestinal tract and 13 patients (0.4%) developed recognizable vitamin K deficiency. There were 33,315 adult admissions and unexpected vitamin K deficiency was diagnosed in 27 (0.08%). It is likely that these figures underestimate the true incidence of vitamin K deficiency because coagulation screening tests were not routinely performed.

The practical importance of these findings is that patients on a poor diet treated with antibiotics may develop vitamin K deficiency within a short period of time. This can lead to serious bleeding, particularly in the postoperative period. We would therefore recommend that vitamin K supplements should be added to the intravenous fluids of patients undergoing major abdominal surgery who are receiving antibiotics.

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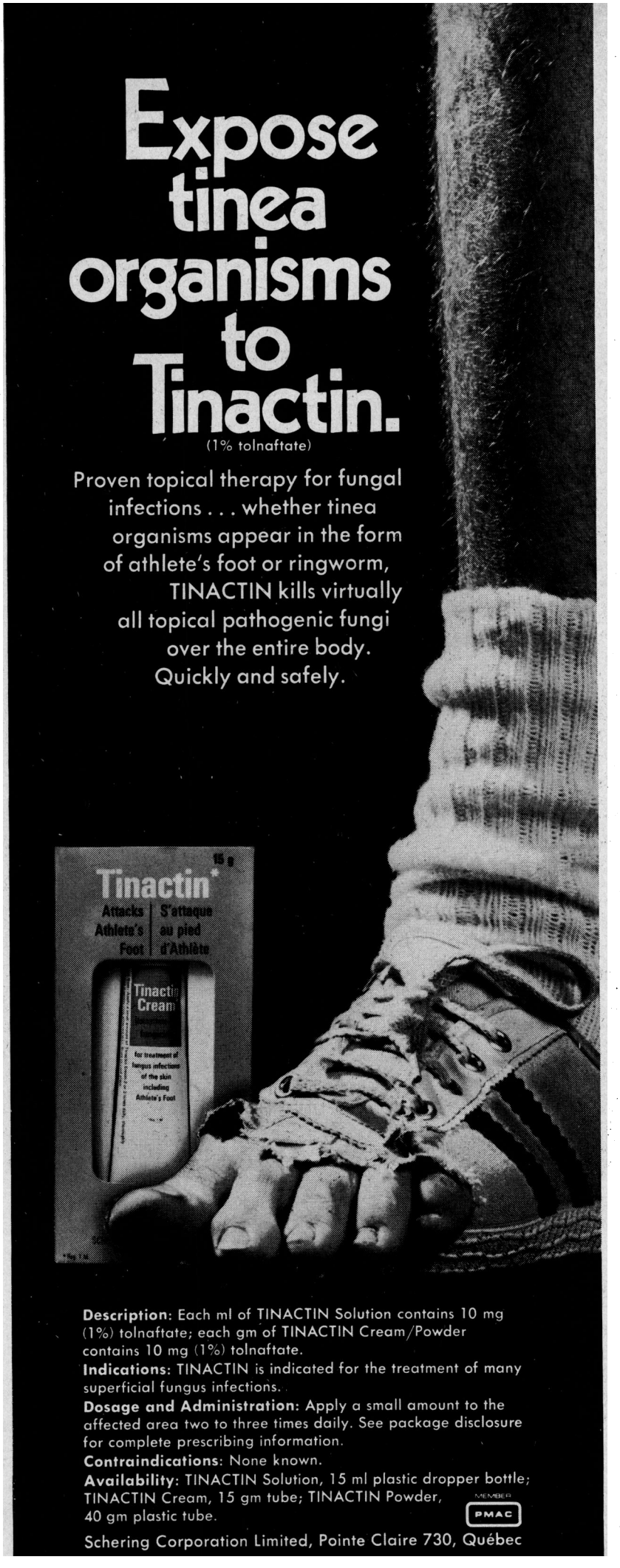

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